UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/684,199 | 10/10/2003 | Malcolm D. McGinnis | 13525 C1 | 5067 |

7590 03/03/2008

David A. Kalow, Esq.
Kalow & Springut LLP
488 Madison Avenue, 19th Floor
New York, NY 10022

| EXAMINER | |
|---|---|
| BABIC, CHRISTOPHER M | |
| ART UNIT | PAPER NUMBER |
| 1637 | |
| MAIL DATE | DELIVERY MODE |
| 03/03/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/684,199 | MCGINNIS ET AL. | |
| | Examiner | Art Unit | |
| | CHRISTOPHER M. BABIC | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10 and 12-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Claims*

Claim(s) 1-10 and 12-16 are pending. The following Office Action is in response to applicant's communication dated December 10, 2007.

### *Specification*

The objection to the specification has been withdrawn in view of applicant's amendment.

### *Claim Objections - Withdrawn*

The objection of claim(s) 10 and 11 has been withdrawn in view of applicant's amendment.

### *Claim Rejections - 35 USC § 112 - Indefiniteness - Withdrawn*

The rejection of claim(s) 10 and 11 has been withdrawn in view of applicant's amendment.

### *Claim Rejections - 35 USC § 102 - Withdrawn*

The rejection of claim(s) 1-3, 15, and 16 over Cocuzza has been withdrawn in view of applicant's amendment. Cocuzza does not teach a polynucleotide mobility-reducing moiety.

The rejection of claim(s) 1-5 and 7-16 over Grossman has been withdrawn in view of applicant's amendment. Grossman does not teach a polynucleotide mobility-reducing moiety.

***Claim Rejections - 35 USC § 103 - Withdrawn***

The rejection of claim(s) 1-5 and 7-16 over Tully and Cocuzza has been withdrawn in view of applicant's amendment. Tully does not teach the "washing" step as optional, or in other words, Tully does not teach running the sequencing reaction mixture directly on an electrophoretic gel.

***Claim Rejections - 35 USC § 103 - New Grounds***

The following rejection(s) is/are made in view of applicant's amendment.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**1. Claim(s) 1-5, 7-10, and 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tully et al. (WO 96/06187 A1; 29 February 1996) in view of Kuppuswamy et al. ("Single nucleotide primer extension to detect genetic diseases: experimental application to hemophilia B (factor IX) and cystic fibrosis genes" Proc Natl Acad Sci U S A. 1991 Feb 15;88(4):1143-7), and in further view of Cocuzza et al. (U.S. 5,484,701).**

With regard to claim(s) 1, Tully teaches methods of multiplex nucleic acid sequencing utilizing primers that comprise a mobility modifying component (pg. 1-6, 11-14, for example). Specifically, Tully teaches methods comprising: (a) contacting a target-specific primer with a polynucleotide sample under conditions effective for the primer to anneal specifically to a primer-complementary region in one or more target polynucleotides, to form one or more target-primer hybrid(s) (pg. 12, ddNTP incorporation step, for example), wherein each target-specific primer contains (i) a target binding segment (end pg. 5, primer sequence, for example) and (ii) a mobility-reducing moiety which does not bind the target (pg. 5-6, 5' nucleotide sequence non-complementary to target, poly(a) or poly(t), for example), (b) reacting said hybrid(s) with a primer extension reagent (pg. 12-13,

ddNTP incorporation step, for example) in the presence of at least two labeled 3'-nucleotide terminators complementary to a selected nucleotide base-type (pg. 12, fluorescent ddNTPs, for example), under conditions effective to for: (i) one or more primer extension products which terminate with at least one labeled 3'-nucleotide terminator (pg. 12, ddNTP incorporation step, for example), and (ii) one or more detectable breakdown products and residual labeled nucleotide terminators (the production of these product is inherent to the sequencing reaction taught by Tully, pg. 12, ddNTP incorporation step, for example).

With regard to claim(s) 3, Tully teaches sequencing reactions that utilize only ddNTPs (middle pg. 3, for example).

With regard to claim(s) 4 and 5, Tully teaches sequencing reactions that utilize 4 different ddNTPs each with its own distinguishable label (middle pg. 3, for example).

With regard to claim(s) 7 and 8, Tully teaches the use of an Applied Biosystems 37 automated sequencer (middle pg. 13, for example).

With regard to claim(s) 10 and 12-14, Tully teaches polynucleotide mobility modifiers of at least 20 additional nucleotides (table 1, for example).

With regard to claim(s) 15 and 16, Tully teaches direct electrophoresis identification reactions without further purification steps after the gel has been run (pg. 13, for example).

Thus, it is clear from the teachings of Tully that additional 5' primer sequences can control primer extension molecule mobility within sieving matrices. Furthermore, it is submitted that the phenomena of smaller products

(e.g. labeled nucleotides) eluting from a sieving matrix at a faster rate (e.g. labeled primer extension products) than larger products was a well-known scientific fact at the time of invention and clearly demonstrated within the teachings of Tully.

With regard to the above claims, Tully does not specifically teach that the electrophoresis conditions contain a denaturant. Furthermore, Tully does teach the "washing" step (fig 2, for example) as optional, or in other words, Tully does not teach running the sequencing reaction mixture directly on an electrophoretic gel.

With regard to the use of denaturants (e.g. urea, formamide, etc.), it is submitted that the use of such chemicals within electrophoretic separation of sequencing reactions was well-known at the time of invention, and often preferred, as they assist in achieving better sequencing results by keeping duplex molecules from forming. Kuppuswamy provides an example of an electrophoresis of a single nucleotide primer extension reaction under denaturing conditions (pg. 1144, col. 1, fig. 1, 8M urea, for example). Thus, it is the position of the examiner that Tully most likely had a denaturant within the disclosed sequencing reaction, and if not, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to incorporate such denaturants into the sequencing reaction of Tully since well-known procedure as demonstrated by Kuppuswamy suggests denaturing conditions as useful in sequencing reactions.

With regard running the sequencing reaction mixture directly on an electrophoretic gel, i.e. without prior washing away of unwanted products, Kuppuswamy expressly teaches the electrophoresis of a single nucleotide primer extension reaction without an intervening "washing" step between the primer extension reaction (pg. 1144-1145, SNuPE, for example) and the electrophoretic separation (pg. 1144, fig. 1, expressly teaches obtaining adequate resolution of extended primer from free nucleotide, for example).

With regard to claimed method as a way of improving sequencing signal by allowing unwanted co-migrating products to elute faster, it is submitted that Cocuzza expressly teaches that the analysis of primer extension products is often complicated by the presence of other reaction components (e.g. unincorporated nucleotides) and that such methods that produce these products would benefit from the removal of such complicating reaction components (col. 1, lines 15-35; col. 5, lines 35-55, for example). Thus, it is clear from the prior art that signal interference from co-migrating products was a well-known problem within the sequencing art at the time of invention. Thus, a skilled artisan would have been motivated to fix this problem.

Thus, in summary, the following facts were known in the art at the time of invention: denaturing conditions within gel matrices helped achieved better sequencing results; an additional polynucleotide strand, non-complementary to the target, could be added to a sequencing primer to control migration through gel matrices; it was beneficial to allow unincorporated nucleotides to elute away from extended primers to obtain adequate resolution within gel matrices.

Therefore, it is the position of the examiner that Tully most likely had a denaturant within the disclosed sequencing reaction, and if not, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to incorporate such denaturants into the sequencing reaction to improve results.

Furthermore, it is the position of the examiner that it would have been *prima facie* obvious to a skilled artisan at the time of invention to apply an additional polynucleotide strand, non-complementary to the target, to sequencing primers, a known technique of migration control, to allow unwanted products of a crude primer extension reaction to elute at a faster rate in order to obtain better resolution of extension products.

In support of the examiner's position, Applicant is directed to *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 80 USPQ2d 1641 (Fed. Cir. 2006), in which the court found that,

> "Our suggestion test is in actuality quite flexible and not only permits, but requires, consideration of common knowledge and common sense,...,Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal—and even common-sensical—we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references,...,Persons of varying degrees of skill not only possess varying bases of knowledge, they also possess varying levels of imagination and ingenuity in the relevant field, particularly with respect to problem-solving abilities."

Thus, the courts have concluded that any reasoned argument grounded in the analysis set forth in *Graham et al. v. John Deere Company of Kansas City et al.*, 148 USPQ 459 (U.S. 1966), may form the basis for a *prima facie* case of obviousness.

In the instant case, a skilled artisan at the time of invention would have been motivated to search for a solution to improve resolution of sequencing gels, i.e. allow for unwanted products to elute at a faster rate in order to obtain better resolution of extension products. The prior art recognizes that migration of sequencing primers through gel matrices can be controlled by adding a polynucleotide strand, non-complementary to the target, the terminus of such primers. Thus, at the time of invention, given the teachings in the prior art, the common knowledge and common sense possessed by a skilled artisan, and the fact that persons of varying degrees of skill not only possess varying bases of knowledge, they also possess varying levels of imagination and ingenuity in the relevant field, particularly with respect to problem-solving abilities, the claimed invention is considered to be the result of ordinary consideration rather than unobvious innovation.

With regard to claim(s) 2, Tully teaches that the use of ddNTPs and dNTPs within sequencing reactions is well-documented (middle pg. 3, for example). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to utilize ddNTPs and dNTPs within the methods of Tully.

With regard to claim(s) 9, it is submitted that radioactive labels were well known in the art at the time of invention as demonstrated by Kuppuswamy (pg. 1145, col. 1, labeled nucleotide, for example). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to incorporate radioactive labels into the sequencing reaction of Tully since well-known procedure as demonstrated by Cocuzza suggests radioactive labels as useful in sequencing reactions.

**2. Claim(s) 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tully et al. (WO 96/06187 A1; 29 February 1996) in view of Kuppuswamy et al. ("Single nucleotide primer extension to detect genetic diseases: experimental application to hemophilia B (factor IX) and cystic fibrosis genes" Proc Natl Acad Sci U S A. 1991 Feb 15;88(4):1143-7), in further view of Cocuzza et al. (U.S. 5,484,701) as applied to claim 1 above, and in further view of Nguyen et al. (U.S. 5,656,145).**

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach slab gel electrophoresis.

Nguyen teaches slab gel electrophoresis, which is widely used in nucleic acid sequencing (col. 1, lines 10-11, for example).

A skilled artisan would have been motivated to apply the slab gel electrophoresis in the methods of Tully and Cocuzza for nucleic acid sequencing

because, as indicated by Nguyen, the slab gel electrophoresis is widely used in nucleic acid sequencing

***Conclusion***

**Claim(s) 1-10 and 12-16 are rejected. No claims are allowed.**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone

number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christopher M. Babic/
Patent Examiner
Art Unit 1637
Technology Center 1600

/Gary Benzion/
Supervisory Patent Examiner, Art Unit 1637